Remarks:

Claim amendments

Claims 26-32 and 34-36, 39 and 48 are pending in the present application.

Claim 34 is amended to recite "said melting point of said second product is so low." The inserted phrase was present in the original claims. The exact claim 34 with the missing phrase was present in the response to a restriction requirement filed on December 15, 2006. The missing phrase was later omitted as a result of an obvious typographical error. No new matter is added to the claim by the amendment. Accordingly, entry of the amendment is respectfully requested.

Claim rejections under 35 U.S.C. §112

Claim 34 was rejected as indefinite. The rejection is obviated by the amendment. The applicants thank the examiner for pointing out the typographical error. In view of the correction of the error, withdrawal of the §112 rejection is respectfully requested.

Claim Rejections under 35 U.S.C. §103

All pending claims were rejected under 35 U.S.C. §103 as obvious over Wittwer et al., U.S. Patent No. 6,174,670 in view of Zimmermann et al., U.S. Patent Application Publication No. 2002/0102548. The rejection is respectfully traversed.

The examiner stated that Wittwer teaches generally amplification and detection of nucleic acids in the presence of a control nucleic acid, and using internally hybridized probes. The control and the target nucleic acids hybridize to the same probe (or probes), with the hybrids having melting points sufficiently different to enable separate detection. It is further stated however, that unlike the applicants' invention, Wittwer does not teach that the control be single stranded and have "only sequences necessary for amplification and binding the detection probe and no more than about 10% of additional sequences."

The examiner then stated that Zimmermann teaches a "synthetically produced single-stranded construct" that serves as an internal control for the amplification assay and is as short as 90 nucleotides. It is further stated that it would have been obvious to combine the method of Wittwer with the short control nucleic acids of Zimmermann.

Without admitting that combining Wittwer with Zimmermann would have been obvious to a person of ordinary skill in the art, the applicants respectfully point out that

the hypothetical combination would fall short of the present invention. Filling the gap between the hypothetical combination and the applicants' invention, would mean further modifying short internal controls taught by Zimmermann. The examiner has not alleged that such further modification would have been obvious. As is shown below, the necessary further modification in fact, would have been ***non-obvious*** under 35 U.S.C. §103.

Specifically, Zimmermann teaches short internal control nucleic acids (approximately 90, 100-400 and preferably 105-200 bp, see [0014]). However, nothing in Zimmermann suggests that the controls have "only sequences necessary for amplification and binding the detection probe and no more than about 10% of additional sequences," as required by the applicants' claims. Nothing in Zimmermann suggests such minimization. Because Zimmermann uses only primers and no detection probes, "sequences necessary for amplification" would be the primer-binding regions only. Since primers generally do not exceed 30 nucleotides, even with the shortest control nucleic acid taught by Zimmermann (90 bp), there would be at least 30 unnecessary nucleotides (90 - 30 x 2 = 30 nt) or 33% (30/90 = 33%). With more common shorter primers, the excess sequences would be even larger: 90 - 20 x 2 = 50 nt or 56%. The actual examples listed by Zimmermann have in excess of 60% unnecessary sequences (controls are 117 and 105 bp long, while the primers are only 20 nt long, 117 – 20 x 2 = 77 nt, 77/117 = 66%). In other words, even when stretched to its hypothetical limits, Zimmermann method exceeds the limitations of the applicants' claims by over three fold (33% vs. 10%). In actual experiments shown in Zimmermann, the limit is exceeded over six fold (66% vs. 10%).

The examiner has not suggested that a leap from 33% to 10% or from 66% to 10% would have been obvious. As is shown below, the suggested modification would be against the express teachings of Zimmermann and Wittwer. The applicants' approach is to nearly eliminate additional sequences in the control nucleic acid. In contrast, Zimmermann devotes efforts to the design and optimization of these unnecessary sequences. The examiner correctly pointed out that in some of the Zimmermann control nucleic acids, the additional sequences are random (Zimmermann, Table 1). This does not negate the fact that Zimmermann devotes effort to design and optimization of the random sequences. Specifically, Zimmermann teaches:

> It is preferable to make use as the standard nucleic acid of a nucleic acid that has the ***greatest possible similarity*** to the nucleic acid that is to be quantified or detected in the sample. This applies in particular to the GC content, the restriction sites, the sequence etc."

[0016], lines 11-15 (emphasis added.) In Table 1, Zimmermann shows control nucleic acids having 77, 63 and 65 bp of additional sequences that underwent such design process

with respect to the different target nucleic acids. The applicants completely dispense with this unnecessary effort. The applicants teach:

> The number of bases for those regions of the control nucleic acid that are neither required for primer binding nor for the probe binding ***is of subordinate importance.*** This is particularly surprising because it has been ***stressed again and again in the prior art*** that control nucleic acids ***should be as similar as possible*** to the nucleic acids to be detected.

Specification, p. 6, lines 24-28 (emphasis added.) MPEP 2145(X)(D)(3) teaches that "proceeding contrary to accepted wisdom is evidence of non-obviousness." In the course of the prosecution of this application, several examples of such prior art emerged. For example, Wittwer, cited in the present office action teaches to approximate the control to the target. *See* Wittwer, col. 45, line 59. Another example is Pasloske, U.S. Patent No. 6,399,307, cited in the prior office action, that teaches elaborate bacteriophage-based control nucleic acids that approximate viral target nucleic acids. *See* Pasloske, Example II (control for HIV) and Example V (control for HCV).

Furthermore, MPEP 2143.01(VI) teaches that "changing a principle of operation" of the prior art is a non-obvious modification. In improving the prior art control nucleic acids, the applicants took a radically new approach. In the prior art control nucleic acids, the principle of operation is having additional sequences (that are not necessary for amplification) as close as possible to the target nucleic acid ("it is preferable [to have] ***greatest possible similarity.***") The applicants' principle is entirely different: to eliminate the additional sequences altogether (sequences are "***of subordinate importance.***") Such a change in principle is a non-obvious modification.

For the foregoing reasons, the combination of Wittwer and Zimmermann does not render obvious the applicants' invention, as claimed in the base claim 48. Reconsideration and withdrawal of the rejection of claim 48 over Wittwer in view of Zimmermann are respectfully requested.

The remaining claims 26-32, 34-36 and 39 depend ultimately on claim 48, and therefore incorporate all the limitations of that claim. Accordingly, withdrawal of the rejections of the dependent claims over Wittwer in view of Zimmermann is also respectfully requested.

Conclusion:

In view of the above, applicants believe that all claims now pending in this application are in condition for allowance. It is believed that no fees are dues at this time.

However, the Commissioner is authorized to charge any additional fee deficiency, or credit any overpayment, to Deposit Account No. 50-0812.

If the Examiner believes that a telephone conference would expedite prosecution of this application, the examiner is invited to call the undersigned directly at the number below.

Respectfully submitted,

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